REMARKS

Initially, Claims 1-3 and 5-9 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At page 3 and 4 of the Office Action, the Examiner suggested that the terms "pharmaceutically" and "pharmaceutical" be deleted from the claims as they represent an implied assertion of therapeutic efficacy.

Applicants point out that they have conducted receptor binding assays. The biological efficacy of compounds believed to be effective as tachykinin receptor antagonists may be confirmed by employing an initial screening assay which measures binding to NK-1 and NK-2 receptor sites. Assays useful for evaluating tachykinin receptor antagonists are well known in the art. See, e.g., J. Jukic, et al. *Life Sciences*, 49:1463-1469 (1991); N. Rouissi, *Biochemical and Biophysical Research Communications*, 176:894-901 (1991); D. Aharony, Isolation and Characterization of Neurokinin A Receptor cDNAs From Guinea Pig Lung and Rabbit Pulmonary Artery. *J. Recept. Res.*, 14:399 (1994). R. Catalioto, Independent Coupling of the Human Tachykinin NK_2 Receptor to Phospholipases C and A_2 in Transfected Chinese Hamster Ovary Cells, *Naunyn-Schmiedeberg's Arch. Pharm.*, 358:395-403 (1998). The antagonist activity at the NK-2 receptor of compounds of the present invention has been determined on the rabbit isolated pulmonary artery and the hamster isolated trachea preparations, two bioassays endowed with two putative NK-2 receptor subtypes. Notwithstanding, to overcome the Examiner's rejection, the terms "pharmaceutically" and "pharmaceutical" have been deleted from the aforementioned claims.

Applicants thank the Examiner for suggestions on amending the claims which are incorporated herein. An Abstract of the Disclosure has been added. In Claim 1, line 1, the term "monocyclic compounds" has been changed to the singular. Claims 1 and 2 have been amended to recite standard Markush language. Further, as suggested by the Examiner, Claims 10-13 have been amended to recite a "method of use" and Claim 15 has been added.

Turning to the substantive matters raised, at page 5 of the Office Action

Claims1-2 were rejected under 35 U.S.C. §103 as being unpatentable over Kitakabake. Specifically, the Examiner stated that Claim 1 excludes the compound cyclo-Val-Val-Phe-Phe but does not exclude three other peptides which thereby renders Claims 1 and 2 obvious.

Applicant respectfully transverses the rejection and requests reconsideration thereof.

Not only does the cited reference fail to disclose the invention as presently claimed, it refers to nonanalogous art. Literature pertaining to peptides for prevention of the gushing of beer is irrelevant for judging the inventiveness of the present NK-2 antagonists. Further, Kitakabake was published in 1979. For the past 22 years, it has not been obvious to modify Kitakabake to produce the compounds of the present invention. In fact, the field of NK-2 receptor antagonists has only developed over the last 10 years with the discovery of the first NK-2 antagonists around 1991.

The present invention is distinctly different from Kitakabake, which does not teach or address main features of the Applicant's invention. Notwithstanding, no teaching is provided that would motivate anyone to modify Kitakabake.

The present invention represents a significant advantage over the prior art and avoids disadvantages of the prior art compositions. The prior art discloses cyclic hexapeptides, bicyclic hexapeptides and cyclic hexapseudopeptides with NK_2 activity. However, there remains a need for more potent and selective NK_2 receptor antagonists. The pA_2 of between 5 and 9 indicates that the compounds of the present invention are potent and selective NK-2 receptor antagonists. These compounds are structurally diverse from the prior art in that they have a lower molecular weight and are monocyclic with only four bifunctional residues linked together via peptide or pseudopeptide bonds. Such activity could not be predicted from the prior art which contains no teaching to suggest same.

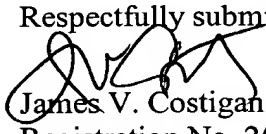
The prior art reference cannot be easily modified to include the unique structural and functional advantages described in the present invention. The elements of the present invention are neither disclosed nor addressed by the prior art.

Accordingly, it is urged that the unique structural and functional composition of the present application is unobvious. Given the aforementioned distinctions, it is maintained that the Kitakabake reference does not teach or suggest the present

invention. For these reasons, it is requested that the rejections to the present claims be withdrawn.

In view of the foregoing, an early and favorable action is earnestly solicited.

Respectfully submitted,



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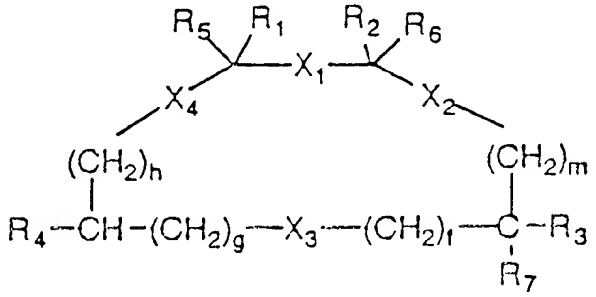
Version with Markings to Show Changes Made:

1. (Amended) A [M]monocyclic compound[s] having the general formula (I):



(I)

in which:

X_1, X_2, X_3, X_4, which may be the same or different from one another, [represent a group chosen from among] is selected from the group consisting of -CONR- , -NRCO-, -OCO-, -COO-, $-CH_2NR-$, $-NR-CH_2-$ [,] and CH_2-CH_2, where R is H or a C_{1-3} alkyl or benzyl;

f, g, h, m, which may be the same or different form one another, represent a number [chosen from among] selected from the group consisting of 0, 1 and 2;

R_1 and R_2, which may be the same or different from one another, represent a $-(CH_2)_r-$ Ar group, where r= 0, 1, 2 and where Ar is an aromatic group [chosen from among] selected from the group consisting of: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, and benzo-imidazole, [the] said Ar group being possibly substituted with a maximum of [2] two residues [chosen from among] selected from the group consisting of C_{1-3} alkyl or halo-alkyl, C_{1-3} alkoxyl, C_{2-4} amino-alkoxyl, halogen, OH, NH_2 [,] and $NR_{13}R_{14}$ where R_{13} and R_{14}, which may be the same or different from one another, represent hydrogen or C_{1-3} alkyl;

wherein R_3 [represents a group chosen from among] is selected from the group consisting of:

-hydrogen,

-linear or branched alkyl having the formula C_nH_{2n+1}, with n= 1-5, cyclo-alkyl or alkylcyclo-alkyl groups having the formula C_nH_{2n-1}, with n= 5-9,

$-(CH_2)_r-Ar_1$ group, where r= 0, 1, 2 and where Ar_1 is an aromatic group [chosen from among] selected from the group consisting of: benzene, naphthalene, thiophene,

benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, and benzo-imidazole, [the] said Ar_1 group being possibly substituted with a maximum of [2] two residues [chosen from among] selected from the group consisting of C_{1-3} alkyl or halo-alkyl, C_{1-3} alkoxyl or amino-alkoxyl, halogen, OH, NH_2 [,] and $NR_{13}R_{14}$, where R_{13} and R_{14}, which may be the same or different from one another, represent hydrogen or C_{1-3} alkyl;

wherein R_4 [represents a group chosen from among] is selected from the group consisting of:

-hydrogen or C_{1-6} alkyl,

- L-Q, where L is a chemical bond or a linear or branched C_{1-6} alkyl residue and Q is [a group chosen from among] selected from the group consisting of:

i) H, OH, OR_9, NH_2, NR_9R_{10}, guanidine, sul[ph]fate, phosphonate[,] and phosphate where R_9 and R_{10}, which may be the same or different from one another, represent a hydrogen C_{1-3} alkyl group, C_{1-3} hydroxyalkyl, C_{1-3} dihydroxyalkyl, C_{1-3}alkyl-$CONHR_{12}$, C_{1-3}alkyltetrazole, C_{1-3}alkyl-COOH or wherein R_9R_{10} joined together form with the N-atom a saturated 4-6 membered heterocycle possibly containing a further heteroatom [chosen in] selected from the group consisting of N, O[,] and S and

wherein R_{12} is a mono-, di-, tri-glycosidic group possibly protected with one or more C_{1-3}-acyl groups or substituted with amino-groups or C_{1-3} acylamino-groups;

ii) COOH, tetrazole, SO_2NH_2, $SO_2NHCOOR_8$, $CONHR_8$, $NHCOR_8$, where R_8 represents a linear or cyclic C_{1-6} alkyl chain containing one or more polar groups [chosen from among] selected from the group consisting of: OH, NH_2, $NR_{15}R_{16}$, COOH, $CONHR_{12}$, PO_3H, SO_3H[,] and OR_{11} and where R_{15} and R_{16}, which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group, and where R_{11} is a C_{1-3} alkyl or C_{2-4} amino-alkyl chain, R_{12} is a mono-, di-, tri-glycosidic group possibly protected with one or more C_{1-3}acyl groups or substituted with amino-groups or C_{1-3}acylamino-groups or $R_{15}R_{16}$ joined together form with the N-atom a saturated 4-6 membered heterocycle possibly substituted with C_{1-3}alkyl-groups or with saturated 4-6 membered heterocycle-groups containing at least an N-atom;

iii) $COOR_{17}$, $CONHR_{12}$, OR_{12} where R_{12} is a mono-, di-, tri-glycoside group possibly protected with one or more C_{1-3} acyl groups or substituted with amine or C_{1-3} acylamine groups and R_{17} is a group R_{12} as above defin[in]ed or a group C_{1-3} alkyl, C_{1-3} alkylphenyl, wherein the phenyl-group can be substituted with a group OH, NO_2, NH_2, CN, CH_3, Cl, Br;

R_5, R_6, R_7, which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group; [their pharmaceutically acceptable salts, their enantiomers and mixture thereof] or an acceptable salt or enantiomer thereof .

2. (Amended) Compounds according to Claim 1, in which:

f, g, h, m, which may be the same or different from one another, may be 0 or 1;

R_1 and R_2 which may be the same or different from one another, represent the side chain of a natural amino acid [chosen from among] selected from the group consisting of tryptophan, phenylalanine, tyrosine[,] and histidine, or the side chain of a non-natural amino acid [chosen in] selected from the group consisting of: tryptophan and phenyl alanine, either mono- or di-substituted with residues [chosen from among] selected from the group consisting of C_{1-3} alkyl or halo-alkyl, C_{1-3} alkoxyl or amino-alkoxyl, halogen, OH, $NH_{2[,]}$ and $NR_{13}R_{14}$, where R_{13} and R_{14}, which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group;

R_3 [represents a group chosen from among] is selected from the group consisting of:

– linear or branched alkyl having the formula C_nH_{2n+1} with n = 1-5 ([chosen in] selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl[,] and t-butyl)

cycloalkyl or alkylcycloalkyl of formula C_nH_{2n-1} with n = 5-9 ([chosen in a] selected from the group consisting of: cyclopentyl, cyclohexyl[,] and methylcyclohexyl)

$-(CH_2)_r$-Ar_1, where r = 1 or 2 and where Ar_1 is an aromatic group [chosen in] selected from the group consisting of: α-naphthyl, β-naphthyl, phenyl, indole, [the] said Ar_1 group being possibly substituted with a maximum of [2] two residues [chosen in] selected from the group consisting of: C_{1-3} alkyl, CF_3, C_{1-3} alkoxyl, Cl, F, OH[,] and NH_2;

R_4 represents an L-Q group where:

L is a chemical bond or CH_2, and

Q is [a group chosen from among] selected from the group consisting of:

– OH, NH_2, NR_9R_{10} [,] and OR_{11}, and where R_9 and R_{10}, which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group, C_{1-3}hydroxy alkyl, C_{1-3}dihydroxyalkyl, C_{1-3}alkyl-$CONHR_{12}$ (wherein R_{12} is a monoglycosidic group derived from D or L pentoses or [hesoxes] hexoses ([chosen in] selected from the group consisting of ribose, arabinose. glucose, galactose, fructose, glucosamine[,] and galactosamine and their N-acetylated derivatives)), C_{1-3}alkyltetrazole, C_{1-3}alkyl-COOH or wherein R_9R_{10} are joined together to form with the N atom a morpholine or a piperidine ring and where R_{11} is a C_{1-3} alkyl chain, or a C_{2-4} amino-alkyl chain;

– $NHCOR_8$ wherein R_8 is a cyclohexane containing from 2 to 4 OH groups, a C_{1-6}alkylchain containing a polar group (chosen in the group consisting of NH_2, COOH, $CONHR_{12}$, (wherein R_{12} is as hereabove defined) or [1,4']bipiperidine)

– COOH, $COOR_{17}$ or $CONHR_{12}$, wherein R_{12} is as hereabove defined and R_{17} is as R_{12} or a group 4-nitrobenzyl.

– R_5, R_6, R_7 are H[.]

in which the carbon atom that carries the substituents R_3 and R_7 has configuration R.

3. A [C]compound[s] according to Claim 2[, as specified below] selected from:

(a) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(b) Cyclo{-Suc-Trp-Phe-[(S)-NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(c) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_{11}$)-CH_2-NH]}

(d) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_4$(4-OCH_3))-CH_2-NH]}

(e) Cyclo{-Suc-Trp(5F)-Phe-[(R)- NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(f) Cyclo{-Suc-Trp(Me)-Phe-[(R)- NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(g) Cyclo{-Suc-Phe(3,4-Cl)-Phe-[(R)- NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(h) Cyclo{-Suc-Trp-Phe(3,4-Cl)- [(R)- NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(i) Cyclo{-Suc-Trp-Tyr-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(j) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_3$-3,4-diCl)-CH_2-NH]}

(k) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_4$-4-OH)-CH_2-NH]}

(l) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-CH_2-C_6H_5)-CH_2-NH]}

(m) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-2-napthyl)-CH_2-NH]}

(n) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-indol-3-yl)-CH_2-NH]}

(o) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-5-F-indol-3-yl)-CH_2-NH]}

(p) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_4-3-F)-CH_2-NH]}

(q) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_3-3,4-diF-CH_2-NH]-}

(r) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_4-4-CF_3-CH_2-NH]-}

(s) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH_2-CH($CH_2C_6H_5$)-NH]}

(t) Cyclo{-Suc-Trp-Phe-[(S)-NH- CH_2-CH($CH_2C_6H_5$)-NH]}

(u) Cyclo{-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-$(CH_2)_3CO$-}

(v) Cyclo{-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-N(CH_3)]-$(CH_2)_3CO$-}

(w) Cyclo{-Suc[1(S)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(x) Cyclo{-Suc[1(R)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(y) Cyclo{-Suc[2(S)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(z) Cyclo{-Suc[2(R)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(aa) Cyclo{-Suc[1(S)-NH(CH_3)]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(ab) Cyclo{-Suc[1-COO(CH_2-C_6H_4-4-NO_2)]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(ac) Cyclo{-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}
[Cyclo{-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}]

(ad) Cyclo{-Suc(1-OH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}

(ae) Cyclo{-Suc(2-COOH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}

(af) Cyclo{-Suc(2-OH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}

(ag) Cyclo{-Suc[1(S)-(2H-tetrazolyl-5-ylmethyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}. TFA

(ah) Cyclo{-Suc[1(S)-(morpholin-4-yl)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}.TFA

(ai) Cyclo{-Suc[1(S)-N(CH_3)$_2$]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}.TFA

(aj) Cyclo{-Suc[1(S)-(piperidin-4-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}.TFA

(ak) Cyclo{-Suc[1(S)-(N(CH_2CH_2OH)$_2$)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-

NH]}.TFA

(al) Cyclo{-Suc[1(S)-(N($CH_2CH(OH)CH_2OH$)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}.TFA

(am) Cyclo{-Suc[1(S)-(3-carboxypropanoyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}.

(an) Cyclo{-Suc[1(S)-[3-N'-ß-D-glucopiranos-1-yl)-carboxamidopropanoyl]amino]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(ao) Cyclo{-Suc[1(S)-[(carboxymethyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}. TFA

(ap) Cyclo{-Suc[1(S)-[N'-ß-D-glucopiranos-1-yl)-carboxyamidomethyl]amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-} TFA

(aq) Cyclo{-Suc[1(S)-(chinyl)amine]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}

(ar) Cyclo{-Suc[1(S)-(4-aminobutanoyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2- NH]-} TFA

(as) Cyclo{-Suc[1(S)-[1,4')bipiperidin-1-yl]acetamido]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-} TFA

(at) Cyclo{-Suc[1-N-(ß-D-glucopiranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}

(au) Cyclo{-Suc[1(S)-[N'-(2-N-acetyl-ß-D-glucopiranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}.

5. (Amended) A [Pharmaceutical] composition[s containing as active the compounds] comprising a compound of general formula (I) according to Claim 1 in combination with a [pharmaceutically acceptable] suitable carrier or excipients.

6. (Amended) A [Pharmaceutical] composition[s] according to Claim 5, [to be used] adapted for use as tachykinin antagonists.

7. (Amended) A [Pharmaceutical] composition[s] according to Claim 6, [to be used] adapted for use as antagonists of the human NK-2 receptor.

8. (Amended) A [Pharmaceutical] composition[s] according to Claim 7, [to be used] adapted for use in the treatment of the bronchospastic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and of the ureter during cystitis, and kidney infections and colics.

9. (Amended) A [Pharmaceutical] composition[s] according to Claim 7, [to be used] adapted for use as anxiolytics.

10. (Amended) [Use of] A method of antagonizing tachykinin in a mammal in need thereof comprising contacting tachykinin peptide receptors with a compound according to Claim 1 for a time and under conditions effective to antagonize said [as] tachykinin [antagonist] receptors.

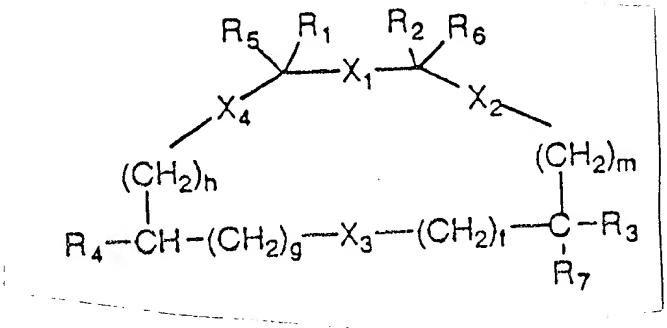
11. (Amended) [Use of] A method of antagonizing an NK-2 receptor in a mammal in need thereof comprising contacting an NK-2 receptor with a compound according to Claim 1 for a time and under conditions effective to antagonize an [as] NK-2 [antagonist] receptor.

12. (Amended) [Use of] A method of antagonizing an NK-2 receptor in a mammal afflicted with asthma comprising contacting an NK-2 receptor with a compound according to Claim 1 for a time and under conditions effective to antagonize an NK-2 receptor [in the treatment of the bronchospastic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and of the ureter during cystitis, and kidney infections and colics] .

13. (Amended) [Use of a composition] A method of antagonizing an NK-2 receptor in a mammal afflicted with an anxiety disorder comprising contacting an NK-2 receptor with a compound according to Claim 1 for a time and under conditions effective to antagonize [as] an NK-2 receptor [antagonist for the treatment of anxiety syndromes] .

ABSTRACT OF THE DISCLOSURE:

Disclosed are monocyclic compounds containing four bifunctional residues linked together via peptide or pseudopeptide bonds of the general formula (I)



(I)

having tachykinin receptor antagonist activity. In particular, compounds of formula I are shown to be neurokinin-2 (NK-2) antagonists useful in the treatment or prevention of disorders of the central nervous system, inflammatory diseases, asthma, or pain.